Topical diphencyprone for alopecia areata: evaluation of 48 cases after 30 months’ follow-up

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Summary
Forty-eight patients (23 male, 25 female) with severe alopecia areata were sensitized and treated with topical diphencyprone. Thirty-eight per cent of the subjects had good regrowth of hair at a mean follow-up period of 30-8 months. The presence of nail changes, a personal history of atopy and a long duration of alopecia had an adverse prognostic effect.

Alopecia areata, with a prevalence of between 0-05 and 0-1%, accounts for approximately 2% of patients presenting to dermatology clinics in Britain and the U.S.A. Extensive alopecia areata is understandably distressing for patients and their embarrassment is compounded by the poor response to current therapies. Patients with severe alopecia are usually highly motivated and keen to participate in novel and experimental treatments. Topical immunotherapy is presently the most effective means to attain hair regrowth in patients with severe alopecia areata.

Diphenylcyclopropenone (diphencyprone, DPC) is currently the preferred contact sensitizer. Unlike dinitrochlorobenzene (DNCB), it has been shown to be non-mutagenic in the Ames test at concentrations of 50 and 100 μg/ml and, in comparison with squaric acid dibutylester (SADBE), is stable in solution. Since 1977, DNCB, SADBE and DPC have been evaluated for the treatment of alopecia areata in a number of studies, overviewed by Naldi et al. in 1990. One problem identified by this group was the failure of studies to assess the long-term overall benefit of treatment. To date, there has been only one study which has followed the progress of patients for more than 1 year (19 months) after treatment with DPC. The aims of this study were to evaluate the longer term follow-up of subjects with severe alopecia areata with topical DPC and to identify possible clinical predictors enabling us to identify those likely to benefit from treatment.

Patients and methods
Ethical Committee approval was sought and obtained. Patients were excluded if they were less than 18 years old, pregnant or likely to become pregnant. Informed written consent was obtained from all patients. Between August 1991 and January 1993, 48 patients (23 male, 25 female) with severe alopecia areata were sensitized and subsequently treated with DPC. DPC was obtained from the Department of Organic Chemistry, University of Nijmegen, Holland and diluted with acetone into appropriate concentrations and aliquots by the Pharmacy Department, Royal Infirmary, Edinburgh.

Because many patients expressed concern that scalp reactions to DPC during sensitization and subsequent challenge treatment would inhibit the wearing of their wigs, we chose to sensitize our patients on the forearm. This also facilitated obtaining biopsy specimens for DPC sensitization studies. Using the forearm all patients became sensitized: an optimal sensitizing regimen was the application of 100 μl of 0-01% DPC in acetone over an area of 2-8 cm. After sensitization, patients were treated with weekly applications of DPC to one side of the scalp, or to one-half of a randomly selected patch of alopecia. DPC was applied carefully with a cotton wool bud on an orange stick by a member of the medical staff, wearing rubber gloves. Some patients attended for weekly DPC application in the department but, if there were geographical difficulties making weekly attendance difficult, we allowed the patient to apply the DPC themselves or with the assistance of a relative provided we were sure they were capable and confident of so doing. A contact telephone number was made available to patients to obtain advice at any time. The patients were advised to keep the area covered for a minimum of 6 h post-treatment and not to wash the scalp for 48 h post-treatment. Once there was evidence of regrowth, DPC application was extended to the remaining areas of alopecia on the scalp. Low concentrations of DPC were
used initially to prevent excess scalp reaction. The concentrations were adjusted individually depending on the severity of the eczematous reaction. A range of concentrations of DPC (0.001, 0.01, 0.025, 0.05, 0.1, 0.2, 0.3, 0.5 and 2%) were available to ensure erythema was maintained on the treated side for 24–36 h post-application, to optimize the chances of regrowth. Bottles of DPC in solution with acetone were returned to the hospital and discarded 3 months after preparation.

The end-point of therapy was hair regrowth. The grading system proposed by MacDonald Hull and Norris was used: grade 1, vellus hair; grade 2, sparse pigmented terminal hair; grade 3, terminal hair regrowth with patches of alopecia; grade 4, growth of terminal hair over all of scalp. The following parameters were also assessed: full blood count, urea and electrolytes, liver function tests, serum ferritin, thyroid function, autoantibody profile and immunoglobulins.

Prognostic factors in relation to DPC therapy were assessed by comparing responders with non-responders under the following categories: (i) sex; (ii) personal history of atopy (asthma, eczema, hay fever); (iii) family history of atopy; (iv) first-degree relative with alopecia areata; (v) duration of alopecia prior to therapy; (vi) type of alopecia at start of DPC therapy; (vii) extent of hair loss; and (viii) presence of nail changes.

Results

Seventy-five per cent of the patients had hair loss on the scalp of greater than 90% and 25% had hair loss between 40 and 90%. The mean age of onset of alopecia areata in the study group was 26.1 years (range 5–64 years) and mean duration of alopecia prior to treatment with DPC was 10–19 years (range 6 months to 36 years).

Forty-seven of the original 48 patients were reviewed. The total observation period was 18–36 months with a mean follow-up period of 30.8 months. Forty-five patients were seen by either PMG or RDA. Two were contacted by telephone and one patient was lost to follow-up. Initial regrowth occurred at a mean of 14.8 weeks in 32 (66.6%) of the subjects. Sixteen of the subjects (33.3%) showed no evidence of regrowth (grade 0), despite the induction of an adequate eczematous response.

Of the 32 responders (i.e. those who initially had shown a grade 1–4 response), nine patients had maintained a cosmetically acceptable regrowth of hair (i.e. total regrowth or sufficient to discontinue use of a wig, if worn) without continuing application of DPC, for a mean follow-up period of 19.8 months (range 12–30 months).

A further nine continued to maintain cosmetically acceptable regrowth of hair with continued application of DPC. All of these patients were using DPC on an intermittent basis (for example, weekly for 2 months) to any new areas of alopecia areata that developed. The mean follow-up in this group was 25.6 months (range 12–31 months).

Nine of the patients had poor hair regrowth despite continued usage of DPC. Six subjects in this group (four males and two females) exhibited the phenomenon of tolerance (an acquired inability to provoke an eczematous challenge reaction on the scalp after successful sensitization) to DPC, despite increasing the concentration applied to the scalp up to a maximum of 2%. Tolerance occurred 7–18 months after starting DPC. The most frequently used concentration of DPC was 0.01%, with 75% of patients using between one and three concentrations of DPC. Twenty-five per cent of the patients required the use of more than four concentrations of DPC to maintain an adequate eczematous response.

The remaining five patients who had initially responded and shown evidence of some regrowth of hair, had to discontinue DPC because of adverse effects. Two patients developed a generalized eczematous response in association with DPC application. Both were women with no history of atopy. Following the discontinuation of DPC and the application of topical steroids, their eczematous eruptions settled rapidly. One patient developed blistering on her forearm at the site of DPC sensitization despite reducing the concentration of DPC applied to the scalp. One patient developed a multiform erythema on her scalp and face necessitating discontinuation of DPC; this may in part have been due to overzealous application of DPC by the patient. One man developed vitiligo at the site of DPC application after 14 months usage. Other adverse effects included mild eczema at the sensitization site on the forearm (95.8%) occurring 24–36 h after application of DPC to the scalp; non-tender cervical lymphadenopathy in 87.5% of the patients, and impaired sleep (due to scalp pruritus on the day of DPC application) in 33.3%. However, none of these adverse effects were considered severe enough by the patients to require time off work, nor did any wish to discontinue DPC because of them.

Of the 16 patients who had not shown any regrowth whatsoever, 15 were reviewed and noted to be unchanged. None of this group had continued to use
DPC. In the 45 patients who had pre- and post-DPC investigations performed, no significant abnormalities were found in haematological, biochemical or immunological indices.

Seventeen (35.4%) had a personal history of atopy (asthma, eczema, hay fever); 20 of the total group (41.6%) had a first-degree relative with atopy; and 10 (22.7%) had a first-degree relative with alopecia areata. Nail changes typical of alopecia areata were noted in 32 (66%) of the patients. Because these different categories may interact, multivariate analysis was performed by logistic regression analysis. Three variables were found to be significant negative prognostic factors: the presence of nail changes (P = 0.01), a personal history of atopy (P = 0.02), and the duration of alopecia (P = 0.04). There was no significant difference between responders and non-responders in this study in relation to sex, age of onset of alopecia areata and type of alopecia at the start of DPC therapy.

Discussion

Topical immunotherapy for severe alopecia areata undoubtedly offers long-term therapeutic hope for some sufferers of this distressing condition. We have shown that after a mean follow-up period of 30.8 months, 18 subjects (37.5% of the original group) had a cosmetically acceptable regrowth of hair which is similar to 43.16% at 19 months, quoted by van der Steen et al. We noted that six of our patients (12.5%) developed tolerance to DPC. In comparison, van der Steen et al. reported tolerance in 10.8%.

We found that nail changes were the most significant adverse prognostic factor. van der Steen et al. also identified this in their short-term follow-up studies, but not in their long-term study. Like MacDonald Hull and Norris, and Tosti et al., we did not find that the type of involvement of alopecia areata prior to DPC conferred prognostic significance, but we established that a long history of alopecia reduced the likelihood of response, in agreement with other authors.

There were a large number of adverse effects but our highly motivated patients tolerated them well. Indeed, only five discontinued treatment with DPC because of adverse effects, and all were disappointed to relinquish the therapeutic opportunity. The most important adverse effect was the development of vitiligo at the site of DPC treatment which, unlike the other adverse effects, persisted despite discontinuing DPC. Vitiligo occurring locally and outside the sites of DPC application has been reported. Hyperpigmentary and hypopigmentary disturbances (dyschromia in confetti) may occur in individuals with darker complexions. The problems of eczema occurring at the arm sensitization site would be overcome by sensitizing on the scalp.

Topical immunotherapy offers hope for some desperate patients with alopecia areata. Patients should be advised about their chances of hair regrowth and warned about the potential adverse effects. In view of the paucity of longer term toxicological studies of DPC we recommend that immunotherapy be reserved for patients with severe alopecia areata, and that treatment be carried out under specialist supervision. Empirically, our current practice is to allow patients to use DPC for up to 3 years. At present the treatment is experimental and further fine tuning is required to reduce the side-effects.

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References

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